Pioglitazone together with imatinib in chronic myeloid leukemia: A proof of concept study

Original Article

Pioglitazone Together With Imatinib in Chronic Myeloid Leukemia: A Proof of Concept Study

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BACKGROUND: We recently reported that peroxisome proliferator-activated receptor γ agonists target chronic myeloid leukemia (CML) quiescent stem cells in vitro by decreasing transcription of *STAT5*. Here in the ACTIM phase 2 clinical trial, we asked whether pioglitazone add-on therapy to imatinib would impact CML residual disease, as assessed by *BCR-ABL1* transcript quantification. **METHODS:** CML patients were eligible if treated with imatinib for at least 2 years at a stable daily dose, having yielded major molecular response (MMR) but not having achieved molecular response 4.5 ($MR^{4.5}$) defined by *BCR-ABL1/ABL1*^{IS} RNA levels $\leq 0.0032\%$. After inclusion, patients started pioglitazone at a dosage of 30 to 45 mg/day in addition to imatinib. The primary objective was to evaluate the cumulative incidence of patients having progressed from MMR to $MR^{4.5}$ over 12 months. **RESULTS:** Twenty-four patients were included (age range, 24-79 years). No pharmacological interaction was observed between the drugs. The main adverse events were weight gain in 12 patients and a mean decrease of 0.4 g/dL in hemoglobin concentration. The cumulative incidence of $MR^{4.5}$ was 56% (95% confidence interval, 37%-76%) by 12 months, despite a wide range of therapy duration (1.9-15.5 months), and 88% of 17 evaluable patients who were still on imatinib reached $MR^{4.5}$ by 48 months. The cumulative incidence of MMR to $MR^{4.5}$ spontaneous conversions over 12 months was estimated to be 23% with imatinib alone in a parallel cohort of patients. **CONCLUSION:** Pioglitazone in combination with imatinib was well tolerated and yielded a favorable 56% rate. These results provide a proof of concept needing confirmation within a randomized clinical trial (EudraCT 2009-011675-79). ***Cancer* 2017;123:1791-9.** © 2016 The Authors. *Cancer* published by Wiley Periodicals, Inc. on behalf of *American Cancer Society*. This is an open access article under the terms of the Creative Commons Attribution NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

KEYWORDS: chronic myeloid leukemia, Imatinib, PPAR gamma agonists, Molecular response.

INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative disorder associated with the t(9;22)(q34;q11.2) translocation and its cytogenetic hallmark, the Philadelphia chromosome (der22). This translocation results in a *BCR-ABL1* fusion gene that codes for a BCR-ABL1 oncoprotein ($p210^{BCR\text{-}ABL}$) with enhanced tyrosine kinase activity. *BCR-ABL1* is present in all cells of the leukemic clone, including leukemic hematopoietic stem cells.[1] The ability of *BCR-ABL1* to induce a similar disease in mice resulted in the design of tyrosine kinase inhibitors (TKIs), a new class of anticancer agents, the first of which was

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imatinib (Gleevec, Novartis Pharmaceuticals).[2] Efficacy and tolerability were determined in the phase 3 IRIS trial,[3] and 15 years later, the long-term survival rate of CML patients in chronic phase receiving continuous TKI therapy closely matches that of the non-CML population.[4]

Residual disease in CML patients is detected by quantifying the *BCR-ABL1* transcripts (*BCR-ABL1/ABL1*) by way of real-time quantitative polymerase chain reaction (RTQ-PCR).[5] Definitions of molecular responses have evolved over the years. Molecular response 4.5 ($MR^{4.5}$) corresponds to a 4.5-log reduction from a standardized baseline (*BCR-ABL1/ABL1* $\leq$ 0.0032% on the International Scale) and represents a reproducible assessment of deep molecular response. Residual CML disease remains detectable above the level of $MR^{4.5}$ in 40% to 90% of patients in spite of sustained imatinib therapy.[6] Patients achieving stable and durable $MR^{4.5}$ may participate in treatment free remission studies. In that patient population, discontinuation of imatinib resulted in molecular relapse in 40% to 60% of patients, depending on the chosen definition of molecular relapse.[7-9] Although their clinical significance is unclear, *BCR-ABL1* positive progenitor cells are found in virtually all patients treated with imatinib, dasatinib, or nilotinib, emphasizing the need to target and control the residual CML stem cell pool in an effort to eradicate the disease.[10-14]

We reported recently that peroxisome proliferator-activated receptor (PPAR)-γ agonists, including the drug pioglitazone, are capable of eroding the CML leukemia stem cell pool in biological assays and 3 anecdotal clinical cases treated for associated type 2 diabetes or off-label.[15] PPAR-γ agonists are currently used as antidiabetic drugs that are not hypoglycemogenic in healthy individuals. Whereas CML stem cells in quiescence resist TKI toxicity, pioglitazone is capable of pulling them out quiescence, thereby sensitizing them to imatinib toxicity.[15] To evaluate the potential therapeutic value of PPAR-γ agonists in CML, we initiated a proof of concept phase 2 study termed ACTIM (actos + imatinib) to score the cumulative incidence of progression from major molecular response (MMR) to $MR^{4.5}$ over 12 months in CML patients who were given pioglitazone in addition to imatinib.

METHODS

Patients and Synopsis of Study Protocol

The ACTIM study is a proof of concept prospective phase 2 trial conducted in centers from the French CML Group. Adult CML patients were eligible if they were 1) in chronic phase, 2) treated with imatinib for more than 2 years with no dose modification within the last 3 months, and 3) in MMR, defined by $BCR\text{-}ABL1/ABL1^{IS} \leq 0.1\%$ without $MR^{4.5}$ at study initiation (see detailed methods in the Supporting Information).

The planned therapy consisted in the continuation of imatinib at the same daily dose per patient (400 mg to 800 mg) with the addition of pioglitazone 30 mg/d during the first 2 months and 45 mg/d thereafter. The study was amended in June 2011 in order to limit the duration of pioglitazone therapy to 12 months and to stop recruitment after completion of the first step of the study. This amendment was requested by the French health regulatory agency (ANSM) after their decision to withdraw pioglitazone from market on the basis of results of epidemiologic studies that suggested an increased risk of bladder carcinoma in patients with diabetes who have had long-term exposure to pioglitazone, although ANSM had granted us a special authorization to continue pioglitazone for ACTIM.[16,17]

Response Definition and Primary Endpoint

The primary endpoint, referred to hereafter as the "molecular response," was the percentage of patients achieving $MR^{4.5}$ by 12 months at 1 or more scheduled determinations, as defined by a *BCR-ABL1/ABL1* ratio of $\leq$ 0.0032% on the International Scale according to the European Leukemia Net recommendations for minimal residual disease quantification.[18] Polymerase chain reaction analysis was centralized at study entry and then molecular assessments were performed in hospital laboratories of the French Quality Control Network for BCR-ABL1 Quantification (Groupe de Biologie Moléculaire des Hémopathies Malignes).

Biomarker Analyses and Secondary Endpoints

Secondary endpoints included 1) safety and efficacy analyses at different time points, 2) measurement of *STAT5* RNA levels, and 3) colony-forming cell (CFC) assays before and during the study (months 6 and 12) (see detailed methods in the Supporting Information). Measurement of $BCR\text{-}ABL1/ABL1^{IS}$ RNA levels was performed every 2 months during the 12 months of study. One patient was lost from follow-up after the study period, and long-term follow-up data were collected.

Statistics

It was necessary to include 24 assessable patients in the first step of the study reported here (see detailed methods in Supporting Information). Because no competing events were recorded, the cumulative incidence of molecular response rate at 12 months, the primary endpoint,

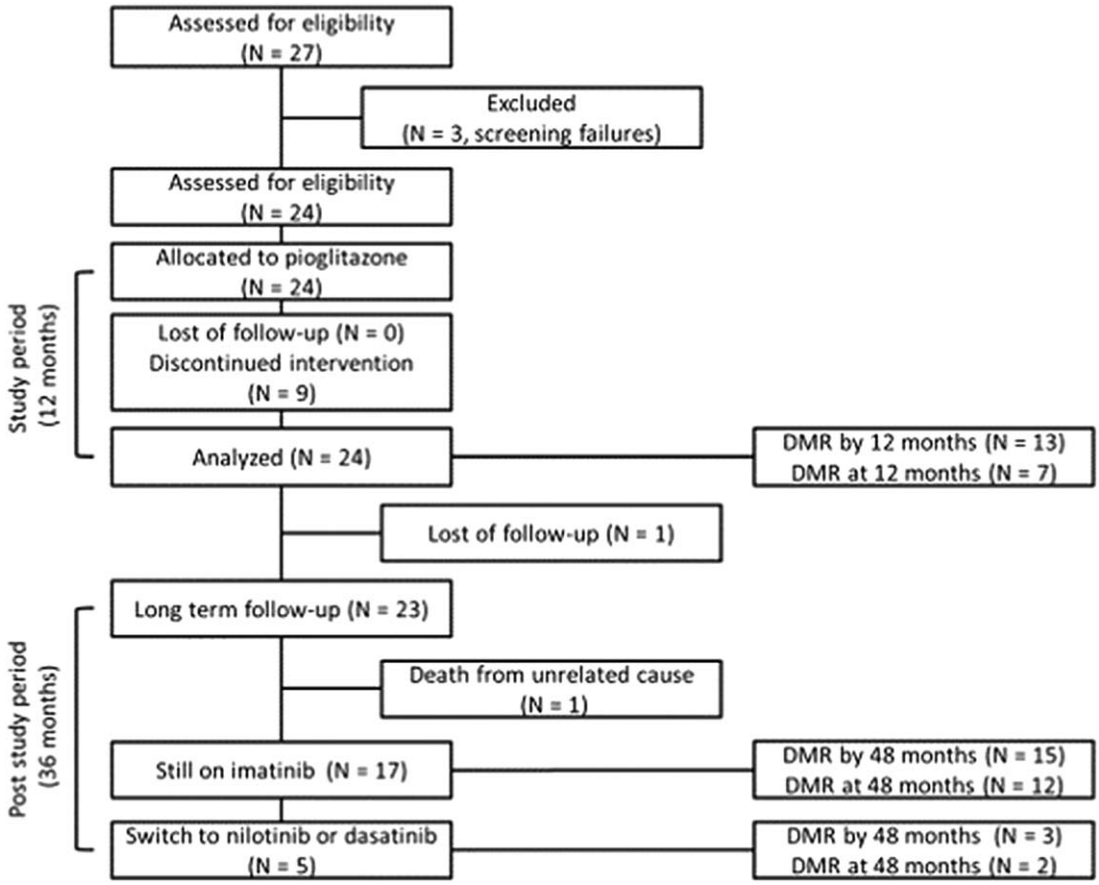

Figure 1. Flow chart outlining the ACTIM study.

was estimated using the Kaplan–Meier method and conducted on an intent-to-treat principle. Additional sensitivity analyses at different time points were then added.

Secondary endpoints regarding patient characteristics and biomarker evolution over time were investigated with the use of paired-sample tests. Cumulative incidences of molecular response rate within subgroups were estimated by the Kaplan–Meier method and compared using the Wilcoxon test. Confidence intervals were estimated at the 95% confidence level, and 2-sided P values $< .05$ were considered to indicate statistical significance. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NJ) and R (The R Foundation for Statistical Computing).

RESULTS

Patient Characteristics

From December 2009 through November 2010, 27 CML patients, all in chronic phase, were recruited and screened. Three patients were in screen failure, 1 patient was already in $MR^{4.5}$ at the screening visit, 1 patient was not in MMR, and 1 patient withdrew consent. None of these patients received pioglitazone. Twenty-four patients were eligible and evaluable (Fig. 1) and were classified on the basis of age, sex ratio, Sokal risk score,[19] time since diagnosis, and quantitative criteria of imatinib therapy (Table 1). Fourteen patients were in MMR without achieving MR^4 (58%) and 10 patients were in MR^4 without achieving $MR^{4.5}$ (42%). Of note, 12 patients were treated with imatinib more than 400 mg/d at inclusion reflecting previous dose adaptations. All these patients were in stable response before inclusion and did not achieved $MR^{4.5}$ previously.

Pioglitazone Administration

All eligible patients started pioglitazone at a dosage of 30 mg/d and increased the dose to 45 mg/d after 2 months of therapy. A total of 9 patients (37.5%) discontinued pioglitazone before month 12. Eight of them did so because their physician–investigator decided to stop pioglitazone administration after France's ANSM issued a

TABLE 1. Patient Characteristics for ACTIM Phase 2 Trial

Characteristic	Value
No. of patients	24
Age, y, median (range)	61 (24-79)
CML phase, % in chronic	100
Sex ratio, men/women	17/7
Sokal score, low/intermediate/high/unknown	13/4/5/2
Time since diagnosis, mo, median (range)	75 (31-174)
Duration of imatinib treatment, mo, median (range)	73 (31-129)
Imatinib daily dose at inclusion, mg/d, median (range)	500 (400-800)
Imatinib [C] min at inclusion, ng/mL, median (range)	890 (437-2436)
Molecular response at inclusion, n (%)	
MMR	14 (58)
MR^4	10 (42)
Pioglitazone treatment duration, mo, median (range)	11.2 (1.9-15.5)
Median pioglitazone daily dose, mg	40
Pioglitazone dosage intensity over 12 months, mg/d	32

report of a possible increased risk of bladder carcinoma. Despite this early termination of pioglitazone, 5 patients achieved $MR^{4.5}$ during the 12-month follow-up period. The first 2 patients included in the study received pioglitazone for longer than 12 months (14.5 and 15.5 months) before the limitation of pioglitazone treatment duration to 12 months. As a result, the median duration of pioglitazone therapy was 11.2 months (range, 1.9-15.5 months). The median cumulative dose of pioglitazone for each patient was 13,957 mg (range, 1710-19,815 mg), which corresponds to a median daily dose of 40 mg; dosage intensity during the 12-month follow-up period for all patients was 32 mg/d (Table 1). No patient had to reduce the dosage of imatinib during the study. Levels of imatinib were not statistically different at inclusion (median dosage, 890 ng/mL [range, 437-2436 ng/mL]) and after 1 month of combined therapy (median dosage, 846 ng/mL [range, 395-2665 ng/mL]; $P = .46$).

Safety

Exploratory analyses were conducted on safety data. A modest decrease in the median value of hemoglobin concentration was observed between inclusion and month 12 (12 g/dL [range, 9.3-14.7 g/dL] vs 11.6 g/dL [range, 9.3-15.1 g/dL]; $P = .03$ [paired *t* test]). The median neutrophil and platelet counts were not different at inclusion compared with month 12 (neutrophils, 2.6 giga/L vs 2.7 giga/L; $P = .11$ [paired *t* test]; platelets, 209 giga/L vs 218 giga/L; $P = .72$ [paired *t* test]).

All patients were monitored with bladder ultrasonography every 6 months during the study period and every 12 months thereafter. No case of bladder carcinoma was reported. Only 1 grade 3 adverse event was recorded (hypokalemia). As expected, no episode of hypoglycemia was recorded. HbA1C and total cholesterol levels were not modified during the 12-month follow-up (Supporting Table 1). Overall, weight was stable over time (median, 81.5 kg at inclusion vs 82 kg at month 12, $P = .27$ [paired *t* test]), although 12 patients experienced a weight gain (grade 1). One patient stopped because of G2 edema. Compared with baseline adverse events before pioglitazone initiation, no significant increase in other adverse events was observed (Supporting Table 2).

Efficacy

Molecular efficacy

Thirteen patients (54%) achieved $MR^{4.5}$ during the 12-month follow-up period (Table 2). Out of the13 patients in MMR and not in MR^4, 4 (30.7%) achieved $MR^{4.5}$ by 12 months. The estimated cumulative incidence of molecular response was 56% (95% confidence interval [CI], 37-76) by 12 months (3 nonresponding patients were evaluated at month 11) (Fig. 2A). Early discontinuation of pioglitazone was not considered a competitive event for molecular response achievement. At 12 months, 7 patients (29.1%) remained in $MR^{4.5}$, whereas 6 patients presented fluctuations of the *BCR-ABL1* transcript around the level of $MR^{4.5}$ before they stabilized (Table 2). Twenty-three out of 24 eligible patients were followed in the long term (median follow-up period, 5.1 years [range, 4.5-5.8 years]). One patient aged 66 years died from multiple myeloma diagnosed after CML 4.5 years after inclusion. At 48 months since inclusion, 14 patients (58.3%) continued to be in $MR^{4.5}$. Focusing on the 17 patients who were evaluable during the follow-up period and who were never switched to another TKI, most of the 12-month nonresponders were able to reach molecular response after the study, so that 15 of those 17 evaluable patients (88.2%) reached $MR^{4.5}$ by 48 months after pioglitazone priming.

Estimation of MMR to $MR^{4.5}$ conversion rates with imatinib alone

Although without the probative value of prospective studies, we estimated the spontaneous rate of MMR to $MR^{4.5}$ conversions in a parallel cohort of CML patients not included in the ACTIM trial with similar characteristics (Supporting Table 3). The cumulative incidence of $MR^{4.5}$ conversions over a 12-month period in this patient population (n = 24), as defined in ACTIM for the

TABLE 2. *BCR-ABL1/ABL1*^{IS} Values in Evaluable Patients Before Inclusion, During Study Period, and During Follow-up Period

	BCR-ABL^{IS} by Real-Time Quantitative Polymerase Chain Reaction (% of ABL1)									
Patient	−6 Months	−3 Months	Inclusion	Months 0-2	Months 2-4	Months 4-6	Months 6-8	Months 8-10	Months 10-12	Best Response During Follow-up (up to 48 Months From Inclusion)
1	*0.018*	*0.012*	*0.004*	0.004	0.007	0.01	**MR$^{4.5}$**	0.008	**MR$^{4.5}$**	MR$^{4.5}$
2[a]	—	—	—	—	—	—	—	—	—	—
3	*0.009*	*0.016*	*0.008*	MR$^{4.5}$	0.011	MR$^{4.5}$	MR$^{4.5}$	MR$^{4.5}$	*0.006*	
4	*0.015*	*0.03*	*0.008*	0.012	MR$^{4.5}$	0.005	MR$^{4.5}$	0.005	*MR$^{4.5}$*	MR$^{4.5}$
5	*0.078*	*0.0133*	*0.012*	0.029	0.03	0.029	0.013	0.014	0.006	MR$^{4.5}$
6[a]	—	—	—	—	—	—	—	—	—	—
7	*0.01*	*0.013*	*0.004*	0.022	0.009	0.006	0.005	0.008	0.009	*0.007*
8	*0.022*	*0.029*	*0.008*	0.019	0.004	0.007	0.016	*0.006*	*MR$^{4.5}$*	MR$^{4.5b}$
9[a]	—	—	—	—	—	—	—	—	—	—
10	*0.07*	*0.08*	*0.1*	0.2	0.1	0.09	0.09	0.19	*0.13*	*0.004*[b]
11	*0.019*	*0.017*	*0.005*	MR$^{4.5}$	MR$^{4.5}$	MR$^{4.5}$	0.007	0.012	MR$^{4.5}$	MR$^{4.5b}$
12	*0.02*	*0.027*	*0.017*	0.039	0.012	0.014	MR$^{4.5}$	0.011	0.009	MR$^{4.5c}$
13	*0.038*	*0.036*	*0.05*	0.021	0.025	0.027	0.015	*0.025*	*0.014*	MR$^{4.5}$
14	*0.012*	*0.004*	*0.004*	0.004	*0.006*	MR$^{4.5}$	MR$^{4.5}$	*MR$^{4.5}$*	*0.008*	MR$^{4.5}$
15	*0.04*	*0.08*	*0.024*	0.030	0.020	0.025	0.1	0.07	*0.07*	MR$^{4.5}$
16	*0.004*	*0.009*	*0.004*	MR$^{4.5}$	MR$^{4.5}$	MR$^{4.5}$	MR$^{4.5}$	*MR$^{4.5}$*	*MR$^{4.5}$*	MR$^{4.5}$
17	*0.108*	*0.083*	*0.051*	0.112	0.107	0.031	0.059	0.119	0.024	MR$^{4.5}$
18	*0.014*	*0.029*	*0.048*	MR$^{4.5}$	0.006	0.01	0.012	0.023	*0.02*	MR$^{4.5}$
19	*0.06*	*0.006*	*0.004*	0.005	0.024	MR$^{4.5}$	MR$^{4.5}$	MR$^{4.5}$	*MR$^{4.5}$*	MR$^{4.5}$
20	*0.04*	*0.02*	*0.07*	0.1	0.07	0.01	0.03	*0.08*	*0.09*	Lost to follow-up
21	*0.008*	*0.004*	*0.009*	0.009	0.004	MR$^{4.5}$	*MR$^{4.5}$*	ND	*0.008*	MR$^{4.5}$
22	*0.03*	*0.013*	*0,021*	0.016	0.021	0022	0.015	0.02	*0.013*	MR$^{4.5b}$
23	*0.06*	*0.09*	*0.04*	0.07	0.041	0.014	0.016	0.11	*0.018*	MR$^{4.5c}$
24	*0.009*	*0.02*	*0.037*	0.008	0.009	0.006	MR$^{4.5}$	0.008	0.015	Loss of MMR[b]
25	*0.027*	*0.01*	*0.01*	0.004	0.005	0.013	0.022	0.01	*0.014*	MR$^{4.5}$
26	*0.018*	*0.012*	*0.015*	0.005	0.016	MR$^{4.5}$	*MR$^{4.5}$*	*MR$^{4.5}$*	*MR$^{4.5}$*	MR$^{4.5}$
27	*0.07*	*0.03*	*0.066*	0.067	*0.097*	*0.096*	*0.034*	ND	*0.064*	MR$^{4.5}$

Abbreviations: MR$^{4.5}$, molecular response 4.5; ND, not done.

MR$^{4.5}$ was defined as *BCR-ABL1/ABL1*^{IS} $\leq$ 0.0032%. Italicized values were obtained before initiation of pioglitazone administration or after its discontinuation.

[a] Not eligible.

[b] Switched to a different tyrosine kinase inhibitor (nilotinib or dasatinib) during follow-up.

[c] Died of unrelated causes.

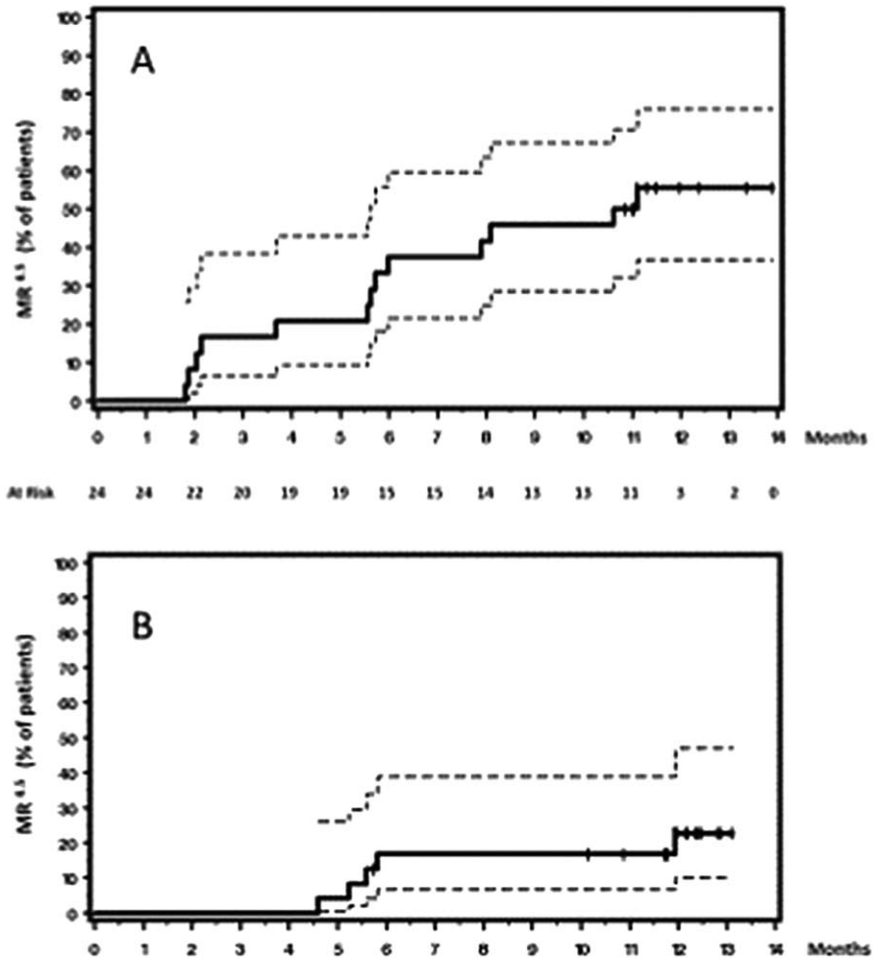

Figure 2. Cumulative incidences of $MR^{4.5}$ progression by 12 months. (A) Thirteen patients (56% [95% CI, 37%-76% (dotted lines)]) included in the ACTIM study achieved $MR^{4.5}$ during the 12-month study period. Median time to $MR^{4.5}$ was 10.6 months [95% CI, 6 months-not determined]. (B) Cumulative incidence of MMR to $MR^{4.5}$ progression by 12 months in a parallel group of CML patients having never received pioglitazone. Patient characteristics were comparable to those in the ACTIM study (Supporting Table 3). Five patients achieved $MR^{4.5}$ during the 12-month follow-up period. The cumulative incidence of $MR^{4.5}$ was 23% (95% CI, 3%-55% [dotted lines]) by 12 months.

molecular response, was estimated to be 23% (95% CI, 3-55) (Fig. 2B).

Associated biological markers

We evaluated biomarkers reflecting pioglitazone exposure. *STAT5* RNA expression levels were assessed in CD34 + cells from bone marrow at inclusion in 18 evaluable patients and during follow-up in 20 patients, including 15 patients with paired analysis at inclusion and at 6 months. *STAT5* RNA levels were expressed relative to *GAPDH*, and median values were 0.129 (range, 0.098-0.266) before and 0.066 (range, 0.016-0.129) 6 months after pioglitazone initiation, showing a reduction in *STAT5* RNA levels after pioglitazone treatment ($P < .0001$ [paired *t* test]) (Fig. 3A). CFC assays with patients' bone marrow CD34 + cells were performed at inclusion, at 6 months after pioglitazone initiation, and at 12 months after pioglitazone initiation in 20, 19, and 5 patients, respectively. The median numbers of colonies were 429 (range, 269-619) at inclusion, 279 (range, 120-566) at 6 months, and 279 (range, 187-300) at 12 months. Paired comparisons at inclusion and at 6 months showed a reduction in clonogenicity ($P = .0003$) (Fig. 3B). We observed a trend for favorable kinetics of $MR^{4.5}$ conversions in patients with the higher percentage of CFC reduction ($P = .044$ by the Wilcoxon test) (Supporting Fig. 1). No significant correlation was evidenced between *STAT5* RNA expression in normal CD34 + cells and molecular response.

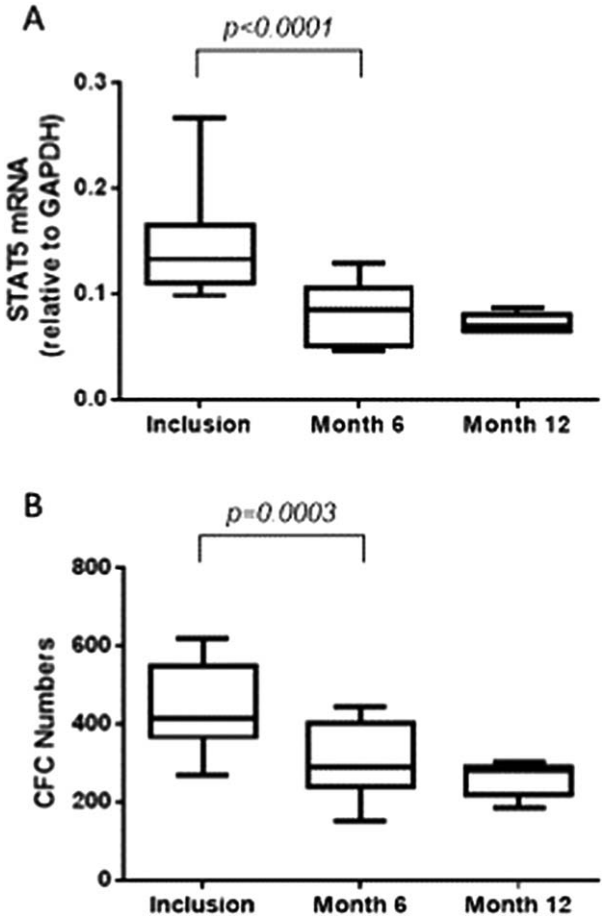

Figure 3. Associated biomarkers *STAT5* and CFC in bone marrow CD34 + cells.Boxes represent the 5th to 95th percentiles; horizontal bars represent the median; vertical brackets represent the ranges. (A) *STAT5* messenger RNA expression relative to *GAPDH* messenger RNA. Number of patients tested: 18 before pioglitazone initiation, 20 at 6 months, and 5 at 12 months. (B) CFC numbers. Number of patients tested: 20 before pioglitazone initiation, 19 at 6 months, and 5 at 12 months.

DISCUSSION

We report here the ACTIM phase 2 trial on the use of the PPAR-γ agonist pioglitazone in addition to imatinib in CML patients not achieving $MR^{4.5}$ with imatinib alone. Pioglitazone was administered at 30 to 45 mg/d, a dose commonly used in type 2 diabetes patients. Overall, patients were exposed to a lower dosage intensity of 32 mg/d. Therapy with pioglitazone was not prolonged over 12 months, as requested by the regulatory agency of France, and some patients interrupted the treatment prematurely. Despite this limitation, progression from MMR to $MR^{4.5}$ was observed in 13 patients (54%), resulting in a cumulative incidence of molecular response of 56% by 12 months. During follow-up after pioglitazone priming, 88% of 17 evaluable imatinib patients reached $MR^{4.5}$ by 48 months, suggesting that the effects of pioglitazone may be delayed.

Because pioglitazone and other PPAR-γ agonists are already approved for the treatment of type 2 diabetes, we anticipate that the biological results we reported recently may influence the management of CML patients by clinicians outside the setting of a clinical trial.[15] This is why we launched the ACTIM phase 2 trial as a proof-of-principle study, although in the absence of a control group of patients, the benefit of pioglitazone in combination with imatinib observed here needs to be confirmed by subsequent randomized studies. However, 2 lines of evidence tend to support the overall conclusion, pending randomized trials. First, patients on ACTIM had a median duration of imatinib therapy of 73 months without having reached $MR^{4.5}$ despite a median daily dose of 500 mg/d; second, our own estimate of the spontaneous rate of MMR to $MR^{4.5}$ progressions in a parallel cohort of CML patients with characteristics closely similar to those of ACTIM was 23%. In agreement with the expected biological effects of pioglitazone,[15] a significant decline in STAT5 transcription and CFC numbers was evidenced in normal bone marrow from CML patients of the ACTIM trial. Interestingly, decreasing CFC levels were positively correlated with favorable kinetics of $MR^{4.5}$ conversions.

Because pioglitazone is well tolerated in most diabetic patients and is not hypoglycemogenic in normal individuals, the only substantial safety concern regarding the use of pioglitazone was the slight increased risk of bladder cancer reported in type 2 diabetes patients with long-term exposure to the drug. However, the increased risk was deemed sufficiently small by the US Food and Drug Administration and other foreign bodies to not suspend the drug's market authorization in light of its expected benefit for the treatment of diabetes.[16,17] Even in France, where the drug has been withdrawn by the regulatory authority, a special authorization was granted to pursue the first step of the ACTIM trial to completion. Importantly, 2 recent epidemiologic studies are now questioning this previous alert by concluding that pioglitazone exposure was not associated with an increased risk of bladder cancer.[20,21] No bladder tumor was detected during follow-up in the ACTIM study.

Other approaches are currently tested in an effort to eliminate CML stem cells. The Hedgehog pathway was targeted by means of smoothened (SMO) inhibitors. Two inhibitors were tested in the clinic, LDE225 and BMS-833923. Their safety profile was not favorable, and no evidence of efficacy was reported.[22,23] Preclinical data on

animal models suggest that inhibiting the Wnt/beta-catenin pathway may also be of interest.[24] Ongoing studies have highlighted targets that are "drugable" with repositioned commercially available compounds such as interferon, arsenic trioxide, or JAK2 inhibitors. The combination of pegylated interferon 2a or 2b to imatinib in patients with newly diagnosed chronic phase CML resulted in higher rates and deeper molecular responses in 2 prospective randomized trial.[25,26] Combined interferon and arsenic treatment was shown to prolong the survival of primary CML mice and to impair severely CML engraftment into untreated secondary recipients, thereby showing a major decrease in CML leukemia initiating cell activity.[27,28] Another approach that targets JAK2 with ruxolitinib together with nilotinib has been reported to enhance the elimination of primary human CML stem cells in vitro, and ongoing clinical investigations are attempting to achieve disease eradication.[29]

In conclusion, the results of the ACTIM study reported here suggest that pioglitazone together with imatinib increases the proportion of CML patients who achieve MR$^{4.5}$, further suggesting that the ability of PPAR-γ agonists to erode the CML stem cell pool may be of clinical benefit for CML patients.[15] The combination was well tolerated and may be continued as long as the *BCR-ABL1* signal remains detectable. The corroborating ACTIW randomized trial is currently recruiting to address the questions that remain, such as the optimal duration of the combination and the ideal PPAR-γ agonist to be used. Discontinuation of both PPAR-γ agonist and TKI while obtaining a high rate of sustained treatment-free remission is currently being tested and would be the ultimate proof of the possibility of CML eradication and cure using this approach.

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CONFLICT OF INTEREST DISCLOSURES

Philippe Rousselot has received research grants from Bristol-Myers Squibb, Pfizer, and Ariad; honoraria from Bristol-Myers Squibb, Ariad, Pfizer, and Novartis; and travel accommodations from Bristol-Myers Squibb and Novartis. Stéphane Prost holds patent #WO 2014/068397 Al. Lydia Roy has received honoraria from Bristol-Myers Squibb, Pfizer, and Novartis and a research grant from Novartis. Gabriel Etienne has received honoraria from Novartis, Bristol-Myers Squibb, and Ariad; has held consulting and advisory roles for Novartis; is on the speaker's bureau for Novartis; and has received travel accommodations from Bristol-Myers Squibb and Novartis. Laurence Legros has received honoraria from Novartis, Bristol-Myers Squibb, Ariad, and Pfizer. Aude Charbonnier has received honoraria from Novartis, Bristol-Myers Squibb, Incyte, and Pfizer. Valérie Coiteux has received honoraria from Novartis, Bristol-Myers Squibb, Ariad, and Pfizer. Pascale Cony-Makhoul has received honoraria from Novartis, Bristol-Myers Squibb, and Pfizer. Francoise Huguet has received honoraria from Amgen, Bristol-Myers Squibb, Incyte, Jazz Pharmaceuticals, Novartis, and Pfizer. Jean-Michel Cayuela has received honoraria from Novartis, Bristol-Myers Squibb, Ariad, Cepheid, Qiagen, and Asuragen. François-Xavier Mahon has received research grants from Bristol-Myers Squibb and Novartis; honoraria from Bristol-Myers Squibb, Pfizer, and Novartis; and travel accommodations from Novartis and Pfizer. François Guilhot has received honoraria from Pfizer and is a consultant for Celgene and Novartis. Philippe Leboulch holds patent #WO 2014/068397 Al.

AUTHOR CONTRIBUTIONS

Philippe Rousselot: Designed the trial and the study; treated patients and collected data; analyzed data and wrote the manuscript. **Stéphane Prost**: Designed the trial and the study; analyzed data and wrote the manuscript; performed biological studies. **Joelle Guilhot**: Designed the trial and the study; analyzed data and wrote the manuscript. **Lydia Roy**: Treated patients and collected data. **Gabriel Etienne**: Treated patients and collected data. **Laurence Legros**: Treated patients and collected data. **Aude Charbonnier**: Treated patients and collected data. **Valérie Coiteux**: Treated patients and collected data. **Pascale Cony-Makhoul**: Treated patients and collected data. **Francoise Huguet**: Treated patients and collected data. **Jean-Michel Cayuela**: Performed biological studies. **Francis Relouzat**: Performed biological studies. **Marc Delord**: Analyzed data and wrote the manuscript. **Heriberto Bruzzoni-Giovanelli**: Treated patients and collected data. **Laure Morisset**: Provided administrative support. **François Guilhot**: Treated patients and collected data. **Philippe Leboulch**: Designed the trial and the study; analyzed data and wrote the manuscript.

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